INTEGRATIVE MOLECULAR CONCEPTS ANALYSIS OF PROSTATE CANCER PROGRESSION

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Similar to other epithelial cancers, prostate cancer progression has been defined histologically as a transition from benign epithelium, to precursor lesions such as high grade prostatic intraepithelial neoplasia (PIN), to adenocarcinoma, and ultimately to metastatic disease. Despite efforts to profile prostate cancer progression using DNA microarrays, the genetic alterations and biological processes that correlate with the observed histological progression are unclear. Using laser capture microdissection to isolate over 100 specific cell populations, we report the profiling of prostate cancer progression from benign epithelium to metastatic disease. By analyzing these expression signatures in the context of 15,000 "molecular concepts", or sets of biologically related genes, we generated a model of prostate cancer progression. Molecular concepts that demarcate critical transitions in prostate cancer progression include protein biosynthesis, ETS family transcriptional targets, androgen signaling, and cell proliferation. Of note, high grade prostate cancer (Gleason Pattern 4) exhibits an attenuated androgen signature relative to low grade prostate cancer (Gleason Pattern 3). Taken together, we demonstrate that analyzing gene expression signatures in the context of a compendium of molecular concepts has utility in understanding disease biology.

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